REMARKS

Claims 1 and 9 were pending. In the Office Action of March 11, 2008, the Examiner rejected claims 1 and 9. Applicants have amended claim 9 to clarify its dependency from claim 1 and added new claim 19; support for the new claim can be found at paragraph [0046] of the U.S. Publication of the present case, U.S. 2006/0100221. No new matter has been added. Accordingly, claims 1, 9, and 19 are pending.

In light of the remarks herein, Applicants respectfully request reconsideration and allowance of the pending claims.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1 and 9 under 35 U.S.C. § 103(a) as being obvious over Willis *et al.* (WO 01/25242, US 6,790,850) (hereinafter "Willis") in view of Berge *et al.* (J. of Pharm. Sciences 1977:1-19) (hereinafter "Berge"). In particular, the Examiner asserted that the presently claimed compound was a structural homolog of a species found in claim 4 of Willis, namely the species 5-[[2,3-difluorophenyl)methyl)thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one, and alleged that a structural homolog was generally of sufficiently close structural similarity to the Willis species that there was a presumption that the presently claimed compound would possess similar properties as the Willis compound. In addition, the Examiner rejected Applicants' prior assertions, including evidence submitted in a Declaration under 37 C.F.R. § 1.132, that the presently claimed compound, a *particular salt*, namely the monosodium salt of 5-[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino)thiazolo[4,5-d]pyrimidin-2(3H)-one, was not an obvious variant of the Willis compound.

The Supreme Court recently clarified that for an invention to be obvious under § 103 requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S.

___ (2007), 127 S. Ct. 1727 (hereinafter "KSR"). However, as the Federal Circuit recently clarified in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1363 (Fed. Cir. 2007), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 2008 WL 2791884 (Fed. Cir. July 2008) (**copies attached**), in order to assert that a compound is obvious over a compound in the prior art, one must: 1) identify a starting reference point or points in the art (*i.e.*, a lead compound), prior to the time of invention, from which a skilled artisan might identify a problem and pursue a potential solution; 2) identify some reason, available within the knowledge of one of skill in the art, to make the *specific molecular modifications* necessary to result in the claimed compound; and 3) identify " some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions." Importantly, in an unpredictable art such as chemistry, *Eisai* confirmed that *KSR*'s focus on "identified, predictable solutions" may present a difficult hurdle because of the genuine unpredictability of the art. Indeed, in *Eisai* the Federal Circuit stated "[i]n other words, post-*KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound."

Here, the Examiner has failed to identify a reason why one having ordinary skill in the art would make the presently claimed compound given the cited Willis and Berge art. In particular, Applicants assert that the Examiner has failed to satisfy the requirements set forth in *Takeda* and *Eisai* for establishing a *prima facie* case of obviousness of a chemical compound. First, the Examiner has failed to make a reasoned identification of a lead compound in the Willis reference. Although the Examiner asserts that the presently claimed compound is an adjacent homolog of a species in Willis, the Examiner provides no reason why one having ordinary skill in the art would pick the Willis compound 5-[[2,3-difluorophenyl)methyl)thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one as a lead compound. There is simply nothing in the Willis reference to point to this compound as a lead compound. Applicants note that the Willis reference discloses a genus of compounds that encompasses a large number of compounds. In fact, 48 specific compounds are exemplified in the Willis reference, with an additional 5 sodium salts and 6 other salts of particular compounds of the 48 exemplified. Accordingly, since the homologous Willis compound has not been reasonably identified as a lead compound, the Examiner has not further identified any reason why one having ordinary skill in the art would then have *any* motivation to make a structural homolog of this *particular* Willis

compound at that particular position, given the large number of other compounds encompassed by the genus and the 47 other compounds exemplified, let alone make the particular monosodium salt as claimed. Clearly the Examiner cannot be asserting that every possible compound of the genus and the 48 particular species set forth in the Willis reference could be a lead compound, and thus that every possible homolog at every possible position and every possible salt is *prima facie* obvious over the Willis and Berge references.

While the Examiner has asserted the structural homolog relationship and the frequency of use of a sodium salt as evidence of a *prima facie* case of obviousness, such evidence presupposes the required reasoned identification of a lead compound, which has not been satisfied in the present case. Moreover, while the Examiner alleges that Berge teaches the use of sodium salts in particular to "achieve better results than the free compound or other salts," Applicants respectfully disagree with the Examiner's characterization of the Berge reference. In fact, Berge states that sodium is the most predominant cation "because of simple availability and physiological reasons." Berge is silent as to whether or not sodium salts would be expected to achieve better results than a free compound or other salts. Applicants note that the Berge reference itself concludes that "selecting a salt form that exhibits the desired combination of properties is a difficult semiempirical choice" and that "only a few generalizations are available to predict the effect of particular salt forms on the characteristics of a drug." Such statements clearly do not support the Examiner's assertions of obviousness, and in fact further bolster the Applicants' rebuttal evidence as set forth in the Declaration under 37 C.F.R. § 1.132, previously submitted. Since the Examiner has failed to establish a *prima facie* case of obviousness over the Willis reference according to the standards set forth in *Takeda* and *Eisai*, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

Double Patenting Rejections

The Examiner rejected claim 1 and 9 on the ground of non-statutory obviousness-type double patenting over claims 1-11 of U.S. Patent 6,790,850 (the Willis reference discussed above). The Examiner also provisionally rejected claims 1 and 9 on the ground of non-statutory obviousness-type double patenting over claims 20-26 of co-pending application 10/863995, a continuation application of the Willis reference. In both cases, the Examiner asserted that the

claimed homologous Willis species 5-[[2,3-difluorophenyl)methyl)thio]-7-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]thiazolo[4,5-d]pyrimidin-2(3H)-one rendered the presently claimed compound obvious. Applicants respectfully disagree for the reasons set forth above. Withdrawal of the rejections is respectfully requested.

The Examiner also provisionally rejected claims 1 and 9 on the ground of non-statutory obviousness-type double patenting over claims 1 and 9 of co-pending application 10/528270 (the '270 application), alleging that the sodium salt species recited in claim 1 of the present application was a positional isomer of the compound in claim 1 of the co-pending '270 application, and that this fact rendered the presently claimed compound obvious. As previously indicated, present claim 1 recites particularly the *monosodium salt* of 5-[[(2,3-difluorophenyl)methyl]thio]-7-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino)thiazolo[4,5-d]pyrimidin-2(3H)-one. Moreover, claim 1 of the '270 application recites a *particular stereoisomer* having 2 stereocenters in the S configuration, namely 5-[[(2,3-difluorophenyl)methyl]thio]-7-{(***1S,2S***)-2-hydroxy-1-(hydroxymethyl)-propyl]amino}thiazolo[4,5-d]pyrimidin-2(3H)-one, rather than a compound of undesignated stereochemistry as referred to by the Examiner in the rejection.

As stated previously, the Examiner has provided no reason for asserting that the '270 application compound would be identified by one having ordinary skill in the art as a lead compound for modification, as is required by *Takeda* and *Eisai*. Moreover, since the '270 compound has not been reasonably identified as a lead compound, the Examiner has not further identified any reason why one having ordinary skill in the art would then specifically modify the '270 compound to result in the presently claimed compound. Simply put, the Examiner has not identified a specific reason why one having ordinary skill in the art would alter a free or generic salt form of a composition to a particular monosodium salt form of a particular positional isomer, and has further failed to identify a reason why one having ordinary skill in the art would alter the particular stereochemistry at two separate stereocenters to result in the claimed composition. Indeed, the multiple steps involved in the allegedly obvious modification (salt, stereochemistry, and positional isomer changes) belie the Examiner's obviousness conclusion.

While the Examiner has asserted the positional isomeric relationship and the frequency of use of a sodium salt as evidence of a *prima facie* case of obviousness, such evidence presupposes

the required reasoned identification of a lead compound, which has not been satisfied in the present case. Moreover, while the Examiner points to the Berge reference to support the assertion that sodium is one of the most frequently employed pharmaceutical cations, Applicants reiterate their previous arguments regarding the teachings of the Berge reference. Therefore, Applicants submit that the Examiner has not made out a *prima facie* case of obviousness over the co-pending '270 application. Withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney if such would expedite prosecution.

Please charge Deposit Account No. 06-1050 for the Petition for Extension of Time fee and for the Request for Continued Examination fee. Please apply any other charges or credits to Deposit Account 06-1050.

Respectfully submitted,

Date: 9/11/08

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HEisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd. C.A.Fed. (N.Y.),2008.

United States Court of Appeals,Federal Circuit.
EISAI CO. LTD. and Eisai, Inc., Plaintiffs-Appellees,
v.
DR. REDDY'S LABORATORIES, LTD. and Dr. Reddy's Laboratories, Inc., Defendants-Appellants, andTeva Pharmaceuticals USA, Inc., Defendant-Appellant.
Nos. 2007-1397, 2007-1398.

July 21, 2008.

Background: Patentee of patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders brought infringement action against competitors. The United States District Court for the Southern District of New York, Gerard E. Lynch, J., 472 F.Supp.2d 493,2006 WL 2872615, granted in part and denied in part owner's motions for summary judgment, and found competitors infringed patent. Competitors appealed.

Holdings: The Court of Appeals, Rader, Circuit Judge, held that:
(1) prior art did not render patent obvious, and
(2) patentee did not commit inequitable conduct in prosecuting patent application for patent.

Affirmed.

West Headnotes

[1] Patents 291 16.13

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.13 k. Fact Questions. Most Cited Cases
Obviousness, for patent law purposes, is ultimately a legal question, based on underlying factual determinations. 35 U.S.C.A. § 103(a).

[2] Patents 291 16(2)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(2) k. Prior Art in General. Most Cited Cases

Patents 291 16(3)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(3) k. View of Person Skilled in Art. Most Cited Cases

Patents 291 36.1(1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k36 Weight and Sufficiency
291k36.1 Secondary Factors Affecting Invention or Obviousness
291k36.1(1) k. In General. Most Cited Cases
The factual determinations underpinning the legal conclusion of obviousness, for patent law purposes, include: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, also known as objective indicia of non-obviousness. 35 U.S.C.A. § 103(a).

[3] Patents 291 324.5

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal

291k324.5 k. Scope and Extent of Review in General. Most Cited Cases
In reviewing a district court's summary judgment of non-obviousness in a patent infringement proceeding, the appellate court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's burden to prove invalidity by clear and convincing evidence. 35 U.S.C.A. § 103(a).

[4] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Where the patent at issue claims a chemical compound, the analysis of the third *Graham* factor for determining obviousness, the differences between the claimed invention and the prior art, often turns on the structural similarities and differences between the claimed compound and the prior art compounds; obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound in a particular way to achieve the claimed compound. 35 U.S.C.A. § 103(a).

[5] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
The requisite motivation to prove the obviousness of a patent claiming a chemical compound based on structural similarity can come from any number of sources and need not necessarily be explicit in the art; rather it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old. 35 U.S.C.A. § 103(a).

[6] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Prior art did not render obvious patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders, where compounds claimed by prior art differed structurally from compound claimed by patent, and the record contained no reasons a skilled artisan would have considered the differences between the compounds identifiable and predictable. 35 U.S.C.A. § 103(a).

[7] Patents 291 ⚿324.54

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.54 k. Presumptions and Discretion of Lower Court. Most Cited Cases

Patents 291 ⚿324.55(2)

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.55 Questions of Fact, Verdicts, and Findings
291k324.55(2) k. Clearly Erroneous Findings. Most Cited Cases
Where a judgment regarding inequitable conduct in prosecuting a patent application follows a bench trial, the appellate court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion.

[8] Patents 291 ⚿97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Inequitable conduct in prosecuting a patent application before the Patent and Trademark Office (PTO) may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submission of

false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive; "materiality," defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence.

[9] Patents 291 ⚿97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
To satisfy the "intent" prong for unenforceability of a patent due to inequitable conduct during the prosecution of a patent application, the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive; gross negligence is not sufficient.

[10] Patents 291 ⚿97

291 Patents
291IV Applications and Proceedings Thereon
291k97 k. Patent Office and Proceedings Therein in General. Most Cited Cases
Patentee did not commit inequitable conduct in prosecuting patent application for patent claiming lead compound used in pharmaceutical approved for the treatment of duodenal ulcers, heartburn, and associated disorders by failing to disclose its own co-pending application, withholding rejections from its co-pending application that also would have applied to patent, failing to disclose prior art, submitting a misleading declaration, and concealing similar compound, where record lacked sufficient evidence of intent to deceive.

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,255,431. Cited as Prior Art.

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
5,045,552. Infringed.

***1355** Joseph M. O'Malley, Jr., Paul, Hastings, Janofsky & Walker, LLP, of New York, New York, argued for plaintiffs-appellees. With him on the brief were Bruce M. Wexler, David M. Conca, Gary G. Ji, and Quinn E. Clancy.
Maurice N. Ross, Budd Larner, P.C., of Short Hills, New Jersey, argued for defendants-appellants Dr. Reddy's Laboratories, Ltd., and Dr. Reddy's Laboratories, Inc. With him on the brief were Andrew J. Miller, Louis H. Weinstein, Ellen T. Lowenthal, and Dmitry V. Sheluho.
Henry C. Dinger, Goodwin Procter LLP, of Boston, Massachusetts, argued for defendant-appellant Teva Pharmaceuticals USA, Inc. With him on the brief were Elaine H. Blais, and David M. Hashmall, Frederick H. Rein, and Emily L. Rapalino, of New York, New York.

Before RADER, LINN, and PROST, Circuit Judges.

RADER, Circuit Judge.
On summary judgment, the United States District Court for the Southern District of New York found in favor of plaintiffs Eisai Co., Ltd. and Eisai, Inc. (collectively Eisai) with respect to the validity and enforceability of U.S. Patent No. 5,045,552 ('552 patent). *Eisai Co. v. Teva Pharms. USA, Inc.*, 472 F.Supp.2d 493 (S.D.N.Y.2006) (*SJ Validity Order*); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, No. 03 Civ. 9053 (S.D.N.Y. Oct. 5, 2006) (*SJ Enforceability Order*). After a bench trial, the district court found that Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. (collectively Dr. Reddy's) and Teva Pharmaceuticals USA, Inc. (Teva) had failed to prove the remaining allegations of inequitable conduct, and that Eisai had established that Dr. Reddy's and Teva infringed Eisai's '552 patent. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, No. 03 Civ. 9053, 2007 WL 1406565 (S.D.N.Y. May 11, 2007) (*Trial Order*). Because the district court correctly determined that the '552 patent

is non-obvious over the proffered prior art and that Eisai's alleged acts during prosecution did not rise to the level of inequitable conduct, this court affirms.

***1356 I**

The '552 patent claims rabeprazole and its salts. Rabeprazole is part of a class of drugs known as proton pump inhibitors, which suppress gastric acid production by inhibiting action of the enzyme H $^{+}K^{+}$ATPase. The distinctions between rabeprazole and its salts are not relevant for this appeal. Therefore this court refers to rabeprazole and its salts collectively as "rabeprazole." Rabeprazole's sodium salt is the active ingredient in Aciphex, a pharmaceutical approved in 1991 by the FDA for the treatment of duodenal ulcers, heartburn, and associated disorders. Aciphex has been a commercial success, garnering over $1 billion in worldwide yearly sales.

Dr. Reddy's and Teva each filed Abbreviated New Drug Applications (ANDAs) under the Hatch-Waxman Act, 21 U.S.C. § 355 and 35 U.S.C. § 271(e), seeking to manufacture a generic version of Aciphex before the expiration of the '552 patent. Because filing an ANDA is an artificial, but legally cognizable, act of patent infringement, *see Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1344 (2004), Eisai filed suit against Dr. Reddy's and Teva. Eisai also sued Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (collectively Mylan), another ANDA filer, but that proceeding was stayed pending the outcome of these actions. Mylan agreed to be bound by the final judgments and any appeals in these cases. *Eisai Co., Ltd. v. Mylan Labs., Inc.*, No. 04 Civ. 656 (S.D.N.Y. Nov. 3, 2004). Both Dr. Reddy's and Teva conceded infringement of claims 1-6 of the '552 patent, but asserted that the '552 patent is unenforceable for inequitable conduct. *Trial Order* at 6-7. Dr. Reddy's stipulated to the validity of all six of the '552 patent's claims, *id.* at 6, but Teva argued before the district court and maintains on appeal that the '552 patent is invalid for obviousness. Both Dr. Reddy's and Teva appeal the trial court's judgments of enforceability. Neither Dr. Reddy's nor Teva appeals the trial court's judgment of infringement. This court has jurisdiction under 28 U.S.C. § 1295(a)(1).

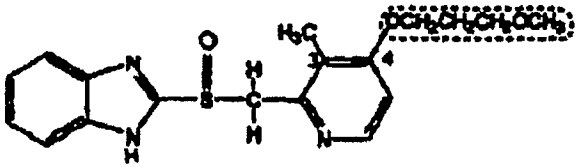
II

[1][2][3] This court reviews a grant of summary judgment without deference. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1362 (Fed.Cir.2003). Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997). The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Thus, in reviewing a district court's summary judgment of non-obviousness, this court reviews the record for genuine issues of material fact without deference, bearing in mind the movant's burden to prove invalidity by clear and convincing evidence. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed.Cir.1998).

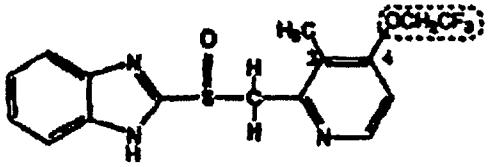
[4][5] Where, as here, the patent at issue claims a chemical compound, the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art ***1357** compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed.Cir.2006) (noting that, for a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions" (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed.Cir.2007). In keeping with the flexible nature of the obviousness inquiry, *KSR Int'l Co. v. Teleflex Inc.*, --- U.S. ----, 127 S.Ct. 1727, 1739, 167 L.Ed.2d 705 (2007), the requisite motivation can come from any number of sources and need not necessarily be

explicit in the art. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed.Cir.2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship ... to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.* (quoting *Dillon*, 919 F.2d at 692).

[6] Teva asserts that a combination of three prior art references renders the '552 patent obvious: 1) European Patent No. 174,726 (owned by Takeda), claiming lansoprazole (EP '726); 2) United States Patent No. 4,255,431 (to Junggren), claiming omeprazole ('431 patent); and 3) an article by Brändström, et al., entitled "Structure Activity Relationships of Substituted Benzimidazoles" (Brändström). EP '726 teaches, inter alia, the ulcer treatment compound lansoprazole. Lansoprazole differs structurally from rabeprazole at the 4-position on the pyridine ring, as indicated in the diagram below. Lansoprazole has a trifluoroethoxy (OCH2CF3) substituent, whereas rabeprazole has a methoxypropoxy (OCH2CH2CH2 OCH3) substituent.



Rabeprazole



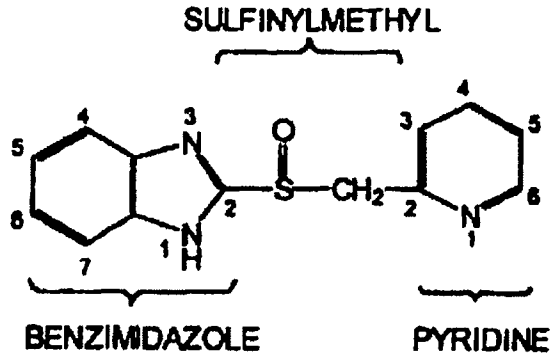
Lansoprazole

Appellant Teva's Br. at 28. Otherwise, the two compounds are identical. *See SJ Validity Order* at 7. Both rabeprazole and lansoprazole are "asymmetrically substituted" with respect to the 4-position on the pyridine ring because the substituent at the 3-position (a methyl group in both compounds) is not the same as the substituent at the 5-position (a hydrogen in both compounds).

The '431 patent discloses a broad class of gastric acid inhibiting compounds, including omeprazole, the first commercial proton pump inhibitor, sold as Prilosec. Although sharing the same basic structure, omeprazole is structurally farther afield from rabeprazole than is lansoprazole. For instance, omeprazole's pyridine ring is symmetrically substituted and has a methoxy (OCH3) group at the 4-position.

Finally, Brändström describes a class of anti-ulcerative compounds having a benzimidazole-sulfinylmethyl-pyridine core (the Brändström core structure):

***1358**



Brändström Core Structure

Rabeprazole, lansoprazole, and omeprazole are all Brändström core structure compounds. Taking the evidence in the light most favorable to Teva, this court assumes that as per EP '726, lansoprazole is twenty times superior to omeprazole for anti-ulcer action, as measured by an indomethacin-induced gastric lesion assay in rats. This court also assumes that lansoprazole has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight, that would have made it desirable to a skilled artisan.

Under these assumptions, one of skill in this art may have considered it a candidate for a lead compound in the search for anti-ulcer compounds. To the contrary, the district court emphasized the differences between anti-ulcer action and gastric acid inhibition. The trial court specifically noted that Teva's expert testified with respect to the EP '726 data that "[t]he level of acid secretion ... from these [anti-ulcer] data ... cannot be determined." *SJ Validity Order* at 13. In this context, this court consults the counsel of *KSR* that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." 127 S.Ct. at 1742. Thus lansoprazole's candidacy as a starting point to develop new anti-ulcer compounds versus new gastric acid inhibitors does not resolve the lead compound analysis, at least not in the absence of any contrary indications. *Cf. Takeda,* 492 F.3d at 1359 (negative side effects could dissuade one of skill from using a particular compound as a starting point).

Nonetheless, as the district court noted, the EP '726 reference teaches at best that the fluorinated substituent of lansoprazole provides "a *special path* to achieving lipophilicity." *SJ Validity Order* at 10 (emphasis in original). And Teva's expert identified a separate reference teaching that fluorine-substituted groups increase lipophilicity. *Id.* The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property. Indeed, Teva's pharmacology expert, Dr. John Forte, declined to opine on lansoprazole's relevance to an examiner assessing the patentability of rabeprazole. J.A. at 14894. And Dr. Reddy's pharmacology expert, Dr. Simmy Bank, testified in deposition that "I thought [lansoprazole] had nothing to do with this trial." J.A. at 14756.

This court notes that the district court did not rigidly limit Teva's obviousness arguments by forcing Teva to select a single lead compound. Rather Teva alone ***1359** selected lansoprazole as the anchor for its obviousness theory, not the district court. In *KSR*, the Supreme Court noted that an invention may have been obvious "[w]hen there [was] ... a design need or market pressure to solve a problem and there [were] ... a finite number of identified, predictable solutions." 127 S.Ct. at 1742 (tense changes supplied to clarify, as the Court stated and as per 35 U.S.C. § 103, that the obviousness inquiry must rely on evidence available "at the time" of the invention, *see Takeda,* 492 F.3d at 1356 n. 2). The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda,* 492 F.3d at 1357 ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions,"127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.,* 520 F.3d 1358, 1364 (Fed.Cir.2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

In other words, post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound. Teva cannot create a genuine issue of material fact on obviousness through the

unsupported assertion that compounds other than lansoprazole might have served as lead compounds. Further, the record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution. In sum, the district court properly concluded that the record did not support a case of obviousness of the '552 patent as a matter of law.

III

[7] As with other summary judgment issues, this court reviews a district court's summary judgment on inequitable conduct without deference. *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1378 (Fed.Cir.2008). In contrast, where a judgment regarding inequitable conduct follows a bench trial, this court reviews the district court's findings of materiality and intent for clear error and its ultimate conclusion for an abuse of discretion. *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1314 (Fed.Cir.2007).

[8][9] Inequitable conduct in prosecuting a patent application before the United States Patent & Trademark Office may take the form of an affirmative misrepresentation of material fact, a failure to disclose material information, or the submission***1360** of false material information, but in every case this false or misleading material communication or failure to communicate must be coupled with an intent to deceive. *Innogenetics*, 512 F.3d at 1378 (citations omitted). Materiality, defined as "what a reasonable examiner would have considered important in deciding whether to allow a patent application," and intent are both questions of fact, and require proof by clear and convincing evidence. *Id.* To satisfy the "intent" prong for unenforceability, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed.Cir.1988) (en banc) (citing *Norton v. Curtiss*, 57 C.C.P.A. 1384, 433 F.2d 779 (1970)). Gross negligence is not sufficient. *Id.* This is a high bar.

[10] On appeal, Teva and Dr. Reddy's allege that Eisai misled the Patent Office in five ways: 1) failing to disclose Eisai's own co-pending '013 application, which claimed the "ethyl homolog" of rabeprazole (compound SHKA 661); 2) withholding rejections from the '013 application's prosecution that also would have been applicable to the '552 patent's prosecution; 3) failing to disclose the prior art "Byk Gulden patent" (WO 8602646); 4) submitting a misleading declaration (the Fujisaki Declaration) to the examiner of the '552 patent; and 5) concealing lansoprazole from the examiner. The district court rejected the fifth assertion on summary judgment, *SJ Enforceability Order* at 58, and the other four after a bench trial, *Trial Order*.

Teva and Dr. Reddy's first and second allegations rely on Eisai's failure to disclose the fact of, and rejections contained in, Eisai's patent application claiming the "ethyl homolog" of rabeprazole. Known to Eisai's scientists as compound SHKA 661, the ethyl homolog differs from rabeprazole as its name suggests. SHKA 661 has one fewer methylene unit at the 4-position of the pyridine ring, giving SHKA 661 an ethoxy group rather than a propoxy group at this position. The district court correctly pointed out that calling SHKA 661 the "ethyl homolog" of rabeprazole in this case could carry a misleading implication with respect to inequitable conduct. The record supplies no evidence to suggest that Eisai's scientists ever referred to SHKA 661 by this name, or thought of SHKA 661 and rabeprazole "primarily in relation to each other." *Trial Order* at 17 n. 7. Rather, the district court found credible the testimony that Eisai scientists considered SHKA 661 separately patentable, even though Eisai ultimately did not pursue that course. *Id.* at 22-23; 42-43. Furthermore, even if a provisional obviousness-type double-patenting rejection might have issued in the prosecution of the '552 patent due to the co-pending SHKA 661 application, the district court found the materiality of this potential situation low, because applicants routinely overcome this type of rejection, *id.* at 44, by amending claims or filing a terminal disclaimer. Nonetheless, the district court did not hold that the fact of the copendency of these two applications to be totally immaterial, accurately noting that applicants should be encouraged to disclose closely related applications. *Id.* at 47.

While disclosure of the co-pending SHKA 661 application to the Patent Office during the prosecution of the '552 patent would have been

prudent, Eisai's failure to do so is by no means fatal, for two reasons. First, the district court had ample evidence from which to conclude that the materiality of the SHKA 611 application ***1361** was low, as outlined above. Second, the record is devoid of any real suggestion of intent to deceive the Patent Office, much less the clear and convincing evidence required to support a finding of inequitable conduct.

As for the rejections of the '013 application that would have been relevant to the prosecution of the '552 patent, the district court did not reach materiality because it discerned insufficient proof of intent to deceive. The district court found the documentary evidence (faxed exchange between Eisai employees Mr. Shuhei Miyazawa, one of the inventors of the '552 patent, and Mr. Mitsuo Taniguchi, Eisai's patent agent, regarding Mr. Miyazawa's presentation to a pharmaceutical trade industry group) to supply no compelling evidence of intent, based on testimony from both parties to the fax. Witness credibility determinations lie squarely within the district court's discretion. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171 (Fed.Cir.2006). The district court was ultimately undisturbed by the Taniguchi/Miyazawa communication based on its evaluation of the witness testimony presented, and this court sees no abuse of discretion. These facts certainly do not rise to the level of "culpability" this court required in *Kingsdown*, 863 F.2d at 876, to establish intent to deceive, or even gross negligence.

Finally, the district court found that Teva's theory that Eisai deliberately hid the ball from the Patent Office by separately filing the '552 and '013 prosecutions to be "implausibly risky," given that such similar applications would usually be assigned to the same examiner in the same art unit. *Trial Order* at 53. The district court thus had ample bases from which to conclude that Eisai's failure to disclose its co-pending '013 application along with the rejections issued in its prosecution, while not completely forthcoming, did not rise to the level of inequitable conduct.

With respect to the Byk Gulden patent, Teva and Dr. Reddy's argue that Eisai's failure to disclose this reference to the Patent Office during prosecution of the '552 patent was material because a reasonable examiner would have used it to issue a new and stronger prima facie obviousness rejection on the basis of Byk Gulden's disclosure of asymmetrically-substituted compounds having a methoxyethoxy at the 4-position of the pyridine ring. But the district court found Byk Gulden's teachings cumulative with references already disclosed to the Patent Office (Junggren or Junggren combined with Beecham). As per 37 C.F.R. § 1.56, cumulative evidence is definitionally not material evidence. *See Monsanto Co. v. Bayer Bioscience N.V.*, 514 F.3d 1229, 1237 (Fed.Cir.2008). Here, the Junggren reference specifically disclosed asymmetrically substituted compounds, including a compound having a 4-position methoxyethoxy substituent. Thus the Byk Gulden reference offered nothing new to the record already before the Patent Office. And even Teva's expert conceded Byk Gulden would not have provided the examiner with anything new. *Id.* at 57. Thus the district court was well within its discretion in concluding that the Byk Gulden patent was not material to the prosecution of the '552 patent. Even if Byk Gulden had been material, the lack of clear and convincing evidence of intent to deceive would nonetheless have imposed an insurmountable bar to finding inequitable conduct, for the reasons given by the district court.

As for the Fujisaki Declaration, Eisai submitted it during prosecution to overcome an obviousness rejection. Because this reference shows rabeprazole's pharmacological properties, the trial court found it highly material. *Id.* at 59. Teva ***1362** and Dr. Reddy's argue that the data presented in the Fujisaki Declaration were misleading. They contend that the comparison with two non-prior art compounds without a comparison of the ethyl homolog of rabeprazole, SHKA 661, sent the examiner on a dead-end side trip. The district court properly characterized this argument as "contorted." *Id.* The Fujisaki Declaration indisputably showed a comparison between rabeprazole and the prior art compound called out by the examiner, demonstrating rabeprazole's superiority. Further, as discussed above, the materiality of SHKA 661 and the patent application claiming it was low. The data from the Fujisaki Declaration were relevant to prosecution, but Eisai had no obligation to include additional, unnecessary data such as a comparison to SHKA 661. Thus the district court did not abuse its discretion in concluding that Eisai did not commit inequitable conduct in failing to include additional data in the Fujisaki Declaration to the examiner. Even here, where the submission to the Patent Office itself was highly material to prosecution, the lack of deceptive

intent rendered stillborn yet another allegation of inequitable conduct.

Finally, Teva and Dr. Reddy's assert that that Eisai deceptively declined to inform the examiner of a patent application for lansoprazole, a prior art proton pump inhibitor (and the active ingredient in Prevacid). The district court disposed of this argument on summary judgment. The district court found that Teva and Dr. Reddy's had presented neither direct evidence of deceptive intent nor any evidence to support an inference of materiality. *SJ Enforceability Order* at 58. The strongest evidence of some problem was the passing comment of one Eisai "insider" that the similarity of lansoprazole and rabeprazole "bothers me." *Id.* at 59. But this vague, subjective statement is not sufficient by any means to establish materiality, let alone intent. Moreover, given lansoprazole's fluorinated substituent and its resultant impotence to render the '552 patent invalid, the district court properly rejected this strained theory of inequitable conduct on summary judgment.

IV

In a series of thoughtful, thorough opinions, the district court carefully explained its reasoning with respect to both obviousness and inequitable conduct. Because the district court properly concluded that Teva and Dr. Reddy's failed to prove that the '552 patent was invalid for obviousness or unenforceable for inequitable conduct, this court affirms the district court's judgment.

AFFIRMED

COSTS

Each party shall bear its own costs.

C.A.Fed. (N.Y.),2008.
Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.
533 F.3d 1353, 87 U.S.P.Q.2d 1452

END OF DOCUMENT

▷Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.
C.A.Fed. (N.Y.),2007.

United States Court of Appeals,Federal Circuit.
TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, INC.,
Plaintiffs-Appellees,
v.
ALPHAPHARM PTY., LTD. and Genpharm, Inc.,
Defendants-Appellants.
No. 06-1329.

June 28, 2007.

Background: Owner of patent for diabetes drug brought infringement actions against proposed manufacturers of generic versions. The United States District Court for the Southern District of New York, Denise Cote, J., 417 F.Supp.2d 341, granted judgment for owner. Manufacturers appealed.

Holdings: The Court of Appeals, Lourie, Circuit Judge, held that:
(1) person of ordinary skill in the art would not have selected closest prior art compound as lead compound for antidiabetic treatment;
(2) person of ordinary skill in the art would not have been prompted to modify closest prior art compound, using steps of homologation or ring-walking, to synthesize claimed compound; and
(3) any error was harmless that district court may have committed by incorrectly implying that prosecution histories were not accessible to public.

Affirmed.

Dyk, Circuit Judge, filed concurring opinion.

West Headnotes

[1] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Person of ordinary skill in the art would not have selected closest prior art compound as lead compound for antidiabetic treatment, and thus presumption of motivation did not apply on competitor's claim of obviousness; although prosecution history of patent included statement characterizing compound as "especially important," any suggestion to select compound was essentially negated given more exhaustive and reliable scientific analysis which taught away from compound and evidence from similar contemporaneously filed patents showed that there were many promising, broad avenues for further research. 35 U.S.C.A. § 103.

[2] Patents 291 ⚿312(4)

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k312 Evidence
291k312(3) Weight and Sufficiency
291k312(4) k. Degree of Proof; Prima Facie Case. Most Cited Cases
Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. 35 U.S.C.A. § 282.

[3] Patents 291 ⚿324.5

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.5 k. Scope and Extent of Review in General. Most Cited Cases

Patents 291 ⚿324.55(4)

291 Patents
291XII Infringement
291XII(C) Suits in Equity

291k324 Appeal
291k324.55 Questions of Fact, Verdicts, and Findings
291k324.55(3) Issues of Validity
291k324.55(4) k. Novelty, Invention, Anticipation, and Obviousness. Most Cited Cases
Whether an invention would have been obvious is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial. 35 U.S.C.A. § 103.

[4] Patents 291 ⚷16(2)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(2) k. Prior Art in General. Most Cited Cases

Patents 291 ⚷16(3)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(3) k. View of Person Skilled in Art. Most Cited Cases

Patents 291 ⚷36.1(1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k36 Weight and Sufficiency
291k36.1 Secondary Factors Affecting Invention or Obviousness
291k36.1(1) k. In General. Most Cited Cases
The factors that control an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of nonobviousness. 35 U.S.C.A. § 103.

[5] Patents 291 ⚷16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
In a case involving a patent on a new chemical compound, some reason must be identified that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound. 35 U.S.C.A. § 103.

[6] Patents 291 ⚷16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Person of ordinary skill in the art would not have been prompted to modify closest prior art compound, using steps of homologation or ring-walking, to synthesize claimed compound in patent for antidiabetic treatment, and thus claimed compound was not obvious, where process of modifying lead compounds was not routine at time of invention, nothing in prior art provided reasonable expectation that adding methyl group to compound would have reduced or eliminated toxicity of lead compound, there was no reasonable expectation in the art that changing positions of substituent on pyridyl ring would have resulted in beneficial changes, and claimed compound differed significantly from lead compound, of which it was not a homolog, in terms of toxicity. 35 U.S.C.A. § 103.

[7] Patents 291 ⚷168(2.1)

291 Patents
291IX Construction and Operation of Letters Patent
291IX(B) Limitation of Claims
291k168 Proceedings in Patent Office in General
291k168(2) Rejection and Amendment of Claims
291k168(2.1) k. In General. Most Cited Cases
Statement made during prosecution of patent for

antidiabetic treatment in response to enablement rejection, indicating only that changes to left moiety of lead compound would create compounds with same properties as compounds of prior art, did not represent that lower toxicity would result from change, for purpose of obviousness claim. 35 U.S.C.A. § 103.

[8] Patents 291 ⚷324.56

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.56 k. Harmless Error. Most Cited Cases
Any error was harmless that district court may have committed by incorrectly implying that prosecution histories were not accessible to public, on competitor's claim of obviousness, where court nonetheless considered prosecution history of patent in its obviousness analysis and accorded proper weight to statements contained therein. 35 U.S.C.A. § 103.

Patents 291 ⚷328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,287,200. Cited as Prior Art.

Patents 291 ⚷328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,340,605, 4,438,141, 4,444,779. Cited.

Patents 291 ⚷328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,687,777. Valid.

***1351** David G. Conlin, Edwards Angell Palmer & Dodge LLP, of Boston, MA, argued ***1352** for plaintiffs-appellees. With him on the brief were Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky; and Anthony J. Viola and Andre K. Cizmarik, of New York, NY. Of counsel on the brief was Mark Chao, Takeda Pharmaceuticals North America, Inc., of Lincolnshire, IL.
Kevin F. Murphy, Frommer Lawrence & Haug LLP, of New York, NY, argued for defendants-appellants. With him on the brief were Edgar H. Haug and Jeffrey A. Hovden.

Before LOURIE, BRYSON, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge LOURIE. Concurring opinion filed by Circuit Judge DYK.

LOURIE, Circuit Judge.
Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. § 103. *Takeda Chem. Indus., Ltd. v. Mylan Labs.*, 417 F.Supp.2d 341 (S.D.N.Y.2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin-a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic

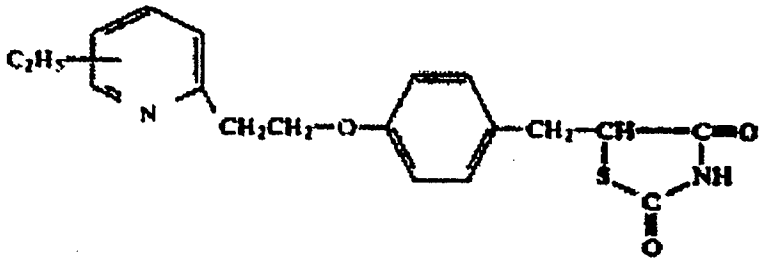
individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes-affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones ("TZDs") was introduced on the market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") first invented certain TZDs in the 1970s. Takeda's research revealed that TZDs acted as insulin sensitizers, *i.e.*, compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPARgamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda*, 417 F.Supp.2d at 348-49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial success since its launch in 1999. By ***1353** 2003, it held 47% of the TZD market, and gross sales for that year exceeded $1.7 billion. *Id.* at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

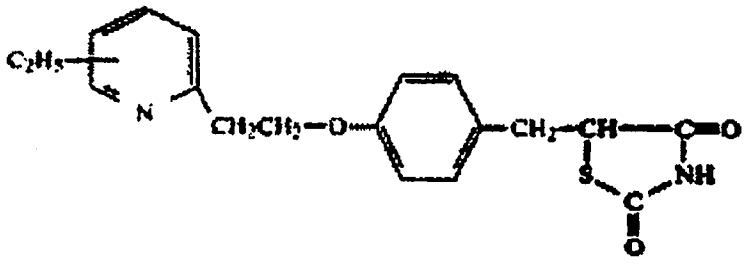
Takeda owns U.S. Patent 4,687,777 (the "'777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." '777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

Id., claims 1 & 5.

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the

molecule, namely, the ethyl-substituted pyridyl ring.[FN1] That chemical structure, which has an ethyl substituent (C^2 H^5) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda*, 417 F.Supp.2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

FN1. Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." *Takeda*, 417 F.Supp.2d at 351.

Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to § 505(j)(2)(B)(ii), asserting that the '777 patent is invalid as obvious under 35 U.S.C. § 103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

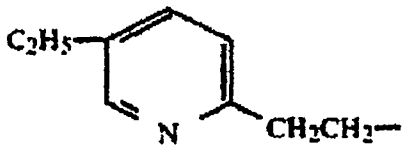
Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103. The court first concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that

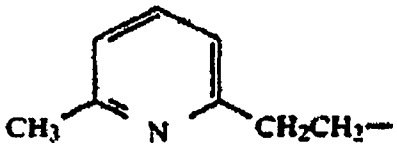
***1354** Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione.

'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:



On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH^3) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured

though inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

[1][2][3] In this appeal, we are presented with one issue, namely, whether the asserted***1355** claims of the '777 patent would have been obvious under 35 U.S.C. § 103 at the time the invention was made. An invention is not patentable, *inter alia,*"if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine,* 344 F.3d 1234, 1238-39 (Fed.Cir.2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.,* 464 F.3d 1286, 1289 (Fed.Cir.2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law, including our en banc decision in *In re Dillon,* 919 F.2d 688 (Fed.Cir.1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

[4] We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.,* --- U.S. ----, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR,* 127 S.Ct. at 1734 (quoting *Graham,* 383 U.S. at 17-18, 86 S.Ct. 684).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided ***1356** by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. Differences Between the Prior Art and the Claims

a. Selection of Compound b as Lead Compound

Alphapharm's first argument challenges the court's

determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed.Cir.1985).

We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed.Cir.1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed.Cir.1984)).

[5] That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[FN2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine***1357** the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

> FN2. We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is determined, we consider that the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

We agree with Takeda and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity.[FN3] Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the

discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

> FN3. The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's U.S. Patent 4,287,200 (the "'200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of millions of TZD compounds." [FN4] *Takeda*, 417 F.Supp.2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in order to show that the claimed compounds of the ' 200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

> FN4. Three divisional applications derive from the '200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the "'779 Patent"). The ' 779 patent is of particular relevance in this appeal and is discussed below. *Takeda*, 417 F.Supp.2d at 378.

***1358** The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the '779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously

with the '779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in ***1359** the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda's witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that *KSR*, as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed.Cir.2007), mandates reversal. Relying on *KSR*, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in *Pfizer*, where we found obvious certain claims covering a particular acid-addition salt, directly supports its position.

We disagree. The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on *Pfizer* fares no better. In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of

this case," we found that the prior art provided ***1360** "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects." Thus, *Pfizer* does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. *See Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 (Fed.Cir.2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

b. Choice of the Claimed Compounds

[6] Even if Alphapharm had established that preliminary finding, and we have concluded that it did not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F.Supp.2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda's experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. *Id.*

Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side effects" and thus researchers would have been inclined "to focus research efforts elsewhere." *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly***1361** from compound b in structure. *Id.* at 376 n. 51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl

compounds.

Alphapharm relies on *In re Wilder*, 563 F.2d 457 (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder*, our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. *Wilder*, 563 F.2d at 460.

We would note that since our *Wilder* decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other,"*Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of Wilder. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F.Supp.2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, Takeda performed***1362** additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

[7] Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the ' 779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra*, the district

court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm ***1363** failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.[FN5]

> FN5. The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a prima facie case of obviousness, and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

2. Scope and Content of the Prior Art

[8] Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 patent prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 patent and the file history that appears in the court's opinion.

We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda,* 417 F.Supp.2d at 378. In considering the prosecution history of the '779 patent, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.*The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b."*Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n. 59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed.Cir.1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

***1364** CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the ' 777 patent have not been shown to have been obvious and hence invalid.

AFFIRMED

Concurring opinion filed by Circuit Judge DYK.DYK, Circuit Judge, concurring.
I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here-claim 2-is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 ("'777 patent")-which are also referenced in the judgment-renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art U.S. Patent No. 4,287,200 ("'200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed.Cir.2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. *See Application of Petering*, 49 C.C.P.A. 993, 301 F.2d 676, 683 (1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed.Cir.2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed.Cir.1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 patent, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

C.A.Fed. (N.Y.),2007.
Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.
492 F.3d 1350, 83 U.S.P.Q.2d 1169

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